UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,599	11/04/2003	Bernd Bohrmann	21459	6499

151 7590 10/27/2006

HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

EXAMINER	
MARTIN, PAUL C	

ART UNIT	PAPER NUMBER
1657	

DATE MAILED: 10/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,599	BOHRMANN ET AL.	
	Examiner	Art Unit	
	Paul C. Martin	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13 and 15-22 are pending in this application and were examined on their merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office Action.

The objections to Claims 4, 6 and 19 have been withdrawn due to the Applicant's amendments to the claims.

The previous rejection of Claim 18 under 35 USC § 112, 2nd paragraph has been withdrawn due to the Applicant's amendment to the claim.

The rejection of Claims 1, 2, 9, 11, 15, 16 and 17 under 35 USC § 103 over Clarke *et al.* (2001) in view of Reik *et al.* (2001) has been withdrawn due to the Applicant's response filed 08/01/06.

The rejection of Claims 1, 2, 4, 7, 8, 9, 11, 13, 18, 19, 21 and 22 under 35 USC § 103 over Clarke *et al.* in view of Reik *et al.* (2001) and Kametani *et al.* (1999) has been withdrawn due to the Applicant's response filed 08/01/06.

The rejection of Claim 3 under 35 USC § 103 over Clarke *et al.* in view of Reik *et al.* (2001) and Kametani *et al.* (1999) and further in view of Schutze *et al.* (1998) has been withdrawn due to the Applicant's response filed 08/01/06.

The rejection of Claim 5 under 35 USC § 103 over Clarke *et al.* in view of Kametani *et al.* (1999) and further in view of Wang *et al.* (1996) has been withdrawn due to the Applicant's response filed 08/01/06.

New Grounds for rejection (not necessitated by Applicant's amendment)

Claim Rejections - 35 USC § 112

Claims 18-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 recites the limitation "the natural and the stable N^{15} isotopes" in step (f). There is insufficient antecedent basis for this limitation in the claim. Claims 19-22 are directly dependant upon claim 18, and because claims 19-22 do not correct the indefiniteness of claim 18, claims 19-22 are additionally found indefinite and also rejected.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 7-8, 10, 11, 13, 15, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kametani *et al.* (1999) in view of Barr *et al.* (1996).

Kametani *et al.* teaches a method for the semi-quantitation of amyloid-β (amino terminal and carboxy terminal) peptides (Pg. 262, Column 2, Lines 3-6 and 49-50) wherein a source of aggregated β-amyloid is obtained from a homogenized brain tissue sample (Pg. 264, Fig.3), an anti-β-amyloid antibody is added, and the precipitated antibody-β-amyloid complex is analyzed using Matrix-Assisted Laser Desorption Ionization/Time-Of-Flight-Mass Spectroscopy (MALDI-TOF) (Pg. 263, Fig. 1).

Kametani *et al.* teaches the preparation for analysis of the isolated β-amyloid by chemical fragmentation and dissolution in a solubilizing agent. (Pg.262, Column 2, Lines 37-46).

Kametani *et al.* teaches the use of synthetically produced β-amyloid (Pg. 262, Column 2, Lines 23-24) and the existence and importance of the N-terminal and amino-terminal forms of β-amyloid (Pg. 262, Column 2, Lines 3-11).

Kametani *et al.* teaches wherein prior to analysis by mass spectroscopy the precipitated β-amyloid is desalted (Pg. 264, Column 1, Lines 1-11 and Column 2, Line 1).

Kametani *et al.* does not teach a method for the absolute quantitation of β-amyloid by providing a source of β-amyloid, adding a defined amount of β-amyloid peptide labeled with a stable isotope to the source, isolating synthetically produced labeled and unlabeled β-amyloid, and determining the amount of β-amyloid present in the source of β-amyloid.

Kametani *et al.* does not teach wherein the isolated β-amyloid is prepared for analysis by mass spectroscopy by enzymatic digestion with a protease selected from the group consisting of endoproteinase Lys-C, trypsin, and endoproteinase Glu-C.

Barr *et al.* teaches an isotope dilution mass spectrometric quantification method of specific proteins wherein a source of apoliprotein A-1 (apo-A1) is combined in solution with a defined amount of synthetically produced apo-A1 peptide labeled with the stable isotope C^{13}, enzymatically digesting the peptides with trypsin, isolating the labeled and unlabeled peptides, analyzing the prepared apo-A1 by mass spectroscopy, and determining the amount of apo-a1 that was present in the source of apo-A1 using the base-line separated peak patterns resulting from the presence of unlabeled and C^{13} labeled proteins (Pg. 1677, Column 2, Lines 50-51 and Pg. 1678, Column 1, Lines 23 and Pg. 1679, Column 1, Lines 14-25 and Pg. 1680, Table 1).

Barr *et al.* teaches that a need exists in the art for a nonepitopic assay with reference capabilities of determining absolute concentrations of a specific protein, that current immunochemical methods based on epitope measurement are often subject to cross-reactivity, weak antibody affinity, or denatured epitopes, and methods based on purification procedures followed by total protein analysis produce variable results that may not be comparable (Pg. 1676, Column 1, Lines 1-2 and Column 2, Lines 1-6) and that a specific need exist for a highly accurate method such as mass spectroscopy to be a point of reference, and that MS had never previously been used to quantify specific proteins (Pg. 1676, Column 2, Lines 6-7 and 20-22).

Barr *et al.* teaches that the new method could be applicable to the measurement of other functional proteins that possess unique peptides (Pg. 1681, Column 2, Lines 44-46), and that ID-MS has the potential to become an important tool in standardizing measurements of other specific proteins quantified in the clinical laboratory (Pg. 1682, Column 1, Lines 4-6).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the method for the semi-quantitation of amyloid-β (amino terminal and carboxy terminal) peptides as taught by Kametani *et al.* with the isotope dilution mass spectrometric quantification method of specific proteins as taught by Barr *et al.* because both methods are drawn to the detection and quantification by mass spectroscopy of specific proteins known to be involved in human diseases.

One of ordinary skill in the art would have been motivated to combine these two techniques because Kametani *et al.* does not teach the absolute quantification of β-amyloid and further utilizes immunochemical methods which were recognized by Barr *et al.* as prone to error. Barr *et al.* discloses that the ID-MS technique itself has broader applicability in the measurement of other proteins and meets a long felt need in the art for a highly accurate nonepitopic assay with reference capabilities of determining absolute concentrations of a specific protein.

It would have been obvious to one of skill in the art at the time of the invention to use synthetically produced isotope labeled β-amyloid in the method of Kametani *et al.* in combination with Barr *et al.* because Barr teaches the use of synthetically produced peptides labeled with stable isotopes in the quantitative method and Kametani *et al.* teaches the use of synthetically produced β-amyloid. One of ordinary skill in the art would have been motivated to use synthetically produced labeled β-amyloid in order to reduce the costs in time and money to produce the synthetically labeled protein by hand in the laboratory. There would have been a reasonable expectation of success in combining these two methods because each is drawn to the detection and characterization of unique synthetically produced proteins by mass spectroscopy.

Claims 1, 2, 4-11, 13, 15, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kametani *et al.* (1999) in view of Barr *et al.* (1996) as applied to claims 1, 2, 4, 7-8, 10, 11, 13, 15, 16 and 17 above, and further in view of Wang *et al.* (1996).

The teachings of Kametani *et al.* (1999) in view of Barr *et al.* (1996) were discussed above.

Neither Kametani *et al.* (1999) nor Barr *et al.* (1996) teach wherein the source of soluble β-amyloid quantified is body fluid or wherein the labeled β-amyloid is recombinantly produced and labeled with a stable isotope.

Wang *et al.* teaches that soluble β-amyloid is found in the cerebrospinal and other biological fluids (Pg. 31894, Column 2, Lines 23-25), the use of recombinantly produced β-amyloid (Pg. 31896, Column 1, Lines 25-30), synthetically produced β-amyloid (Pg. 3895, Column 1, Lines 75-76) and the quantitative analysis of immunoprecipitated β-amyloid using MALDI-TOF spectroscopy (Pg. 31895, Column 1, Lines 67-73).

It would have been obvious to one of ordinary skill in the art at the time to combine the methods for the semi-quantitation of amyloid-β (amino terminal and carboxy terminal) peptides as taught by Kametani *et al.* with the isotope dilution mass spectrometric quantification method of specific proteins as taught by Barr *et al.* with the use of soluble β-amyloid is found in the cerebrospinal and other biological fluids and the use of recombinantly produced β-amyloid because Kametani *et al.* teaches the use of the soluble form of β-amyloid peptides in their method and one of skill in the art would have recognized that the use of alternate sources of β-amyloid would have been desirable based upon the economics and availability of particular β-amyloid sources. One of ordinary skill in the art would have recognized that the use of a recombinantly produced labeled β-amyloid would have been seen as a functional variation on the synthetically produced β-amyloid as described by Kametani *et al.* above; while the labeling of the recombinant β-amyloid would have been an obvious functional variation on the isotope labeling of the proteins used in the method of Barr *et al.* above. One of ordinary skill in the art at the time of the invention would have been motivated to use body fluids as a source of soluble β-amyloid and recombinantly produced labeled β-amyloid based upon the availability of β-amyloid sources and the economics associated with obtaining appropriate standards.

There would have been a reasonable expectation of success in making these adaptations because Kametani *et al.* teaches the use of synthetically produced soluble β-amyloid in a semi-quantitative mass spectroscopy assay of a tissue sample and Wang *et al.* teaches the use of both synthetically produced and recombinantly produced soluble β-amyloid for use in a quantitative mass spectroscopic assay of β-amyloid.

Claims 1-4, 7, 8, 10, 11, 13, and 15-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kametani *et al.* (1999) in view of Barr *et al.* (1996) as applied to claims 1, 2, 4, 7-8, 10, 11, 13, 15, 16 and 17 above, and further in view of Schutze *et al.* (1998).

The teachings of Kametani *et al.* and Barr *et al.* (1996) were discussed above.

Neither Kametani *et al.* nor Barr *et al.* teaches wherein the source of β-amyloid deposits are obtained from a tissue sample by laser dissection microscopy.

Neither Kametani *et al.* Barr *et al.,* Schutze *et al.* nor Wang *et al.* teach a method for the quantification of amyloid-β in a sample by providing excised amyloid deposits from mammalian brain samples containing aggregated amyloid-β, adding a defined amount of amyloid-β peptide labeled with a stable isotope, dissolving the excised aggregated beta amyloid in the presence of the labeled amyloid-β, digesting the dissolved amyloid-β with a protease, analyzing the digested amyloid-β peptide mixture by mass spectroscopy, and determining the amount of amyloid-β present in the source of aggregated or soluble amino or carboxy amyloid-β using the base-line separated peak patterns resulting from the presence of the labeled and unlabeled peptides in the sample.

Schutze *et al.* teaches the use of laser dissection microscopy to capture samples of any shape and size including cell clusters and single cells. (Pg. 737, Column 1, Lines 38-40 and Column 2, Lines 1-2) and laser dissection microscopy avoids mechanical contact to capture clean samples of any shape and size (Pg. 737, Column 1, Lines 38-40).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the methods for the semi-quantitation of amyloid-β (amino terminal and carboxy terminal) peptides from a brain tissue sample as taught by Kametani *et al.* with the isotope dilution mass spectrometric quantification method of specific proteins as taught by Barr *et al.* because one of ordinary skill in the art would have recognized that the method of obtaining the amyloid deposits does not patentably change the method of Claim 1, i.e., the amyloid deposits are analyzed whether excised by tissue biopsy or by laser dissection microscopy unless there is a demonstrable unexpected result. The ordinary artisan would have been motivated to modify the methods of Barr *et al.* and Kametani *et al.* with the addition of the laser dissection microscopy technique because the high degree of accuracy over conventional dissection methods would enable the artisan to excise more completely those minute areas of tissue containing β-amyloid to be examined with less contamination from surrounding tissue and maintain the integrity of the tissue section. As the technique had been practiced with success by other Researchers, and does not materially change the method of Claim 1, the ordinary artisan would have had a reasonable expectation of success in combining this technique with those of Barr *et al.* and Kametani *et al.* unless there is evidence to the contrary or of an unexpected result.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the method for the semi-quantitation of soluble amyloid-β (amino terminal and carboxy terminal) peptides as taught by Kametani *et al.* wherein a source of aggregated β-amyloid is obtained from an excised homogenized human brain tissue sample, an anti-β-amyloid antibody is added, and the precipitated antibody-β-amyloid complex is analyzed using Matrix-Assisted Laser Desorption Ionization/Time-Of-Flight-Mass Spectroscopy (MALDI-TOF) with the isotope dilution mass spectrometric quantification method of specific proteins method of Barr *et al.* wherein a defined amount of synthetically produced apo-A1 peptide labeled with the stable isotope C^{13}, enzymatically digesting the peptides with trypsin, isolating the labeled and unlabeled peptides, analyzing the prepared apo-A1 by mass spectroscopy, and determining the amount of apo-a1 that was present in the source of apo-A1 using the base-line separated peak patterns resulting from the presence of unlabeled and C^{13} labeled proteins because one of skill in the art would have recognized that this would allow the absolute quantification of soluble or aggregated β-amyloid in a tissue sample. One of skill in the art would have been motivated to make these changes because of the expected benefits and advantages discussed by Barr *et al.* namely the higher degree of accuracy of ID-MS over the methods of the prior art and its applicability to many other proteins.

The use of excised amyloid deposits would have been recognized as an obvious variation on the excised tissue sample used by Kametani *et al.* and does not materially change the method or composition of the invention. There would have been a reasonable expectation of success in combining these methods because of the similarity in direction of the two methods, namely the quantitative comparison between mammalian proteins using mass spectroscopy.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
Examiner
Art Unit 1657

10/19/06

Jon Weber
Supervisory Patent Examiner